**INTERVIEW SUMMARY**

Applicants would like to take this opportunity to thank the Examiner for the courtesy extended during the interview held on April 6, 2005. In accordance with the discussions held at the interview, Applicants have amended the claims and present additional evidence in support of the following amendments expected to place this application in condition for allowance. During the course of the interview, the Examiner agreed that the amendments and evidence presented herein would place the pending claims in condition for allowance.

During the interview, the claimed invention and its distinguishing features over the prior art were discussed at length. The applicant pointed out that the "early" references cited in the Office Action represent an outdated line of thinking premised on an expectation of therapeutic effect which was found to be incorrect upon further testing. At that time, it was expected that certain *in vivo* effects could be predicted from the *in vitro* data presented in the references. On the contrary, the *in vitro* data presented in the references was not predictive of the *in vivo* effects. In fact, the *in vivo* data presented in the "later" publications presented at the interview and discussed below demonstrates that one of ordinary skill in the art, at the time the present application was filed, could

**not** have reasonable expected success for therapeutic effectiveness. Thus, the inventive subject matter is thus both surprising and non-obvious over the prior art, taken as a whole at the time the present application was filed.

**REMARKS**

Claims 1-18 were pending in this application, claims 1 and 2 have been amended, and new claims 19-26 have been added. There are now three independent claims and a total of 26 claims, A check for six extra claims in excess of 20 total claims is attached.

The amendments to the claims do not introduce new matter within the meaning of 35 U.S.C. §132. Basis for the claim amendments is found on page 6, lines 8-17; page 7, lines 17-26; in claims 1-18 as originally filed; and elsewhere throughout the specification and claims. Accordingly, entry of the amendments is respectfully requested.

The Examiner is thanked for withdrawing the objections to the specification and the rejections of claims 7, 9, 15, and 17 under 35 U.S.C. §112, second paragraph in light of the amendments made in the Response filed October 4, 2004.

**1. Rejection of Claims 1, and 8-10 under 35 U.S.C. §102(b)**

Claims 1 and 8-10 stand rejected under 35 U.S.C. §102(b) as being anticipated by Levy, et al. (U). This rejection is traversed in so far as the present claims are conceived, on the basis that Levy does not enable the teaching of the *in vivo* effect or treatment.

As the basis for this rejection, the Office Action states:

> Applicant claims a method for treating a disease selected from diabetes mellitus and atherosclerosis comprising administrating to a subject an effective amount of crude *Dunaliella* powder comprising an approximately 1:1 ratio of all-trans and 9-cis β-carotene.
>
> Applicant's main argument is directed to the idea that the method of treatment taught by Levy does not encompass the limitation of newly amended Claim 1 comprising "the use of *Dunaliella* powder comprising an approximately 1:1 ratio of all-trans and 9-cis β-carotene". However, Applicant's argument is not found persuasive because on page 55, Column 2, under "Supplements", Levy clearly teaches the use of an encapsulated *Dunaliella* powder comprising the claim-designated ratio of ingredients. For example, Levy expressly teaches, "The β-carotene was comprised of two major isomers: all-trans (42%) and 9-cis (43%), [citation omitted]". Moreover, Levy teaches a method of treating patients suffering from diabetes mellitus and at high risk of developing atherosclerosis comprising administering an effective amount of an extract obtained from *Dunaliella bardawil* in encapsulated form. Levy teaches that the administration of the algal extract inhibited the oxidation of LDL derived from diabetic patients.

To constitute anticipation under 35 U.S.C. §102, all material elements of a claim must be found in one enabled prior art source. In re Marshall, 577 F.2d 301, 198 USPQ 344 (CCPA 1978); In re Kalm, 378 F.2d 959, 154 USPQ 10 (CCPA 1967).

Claim 1 is directed to the treatment of diabetes mellitus by administration of an effective amount of crude *Dunaliella* powder. Contrary to the Office Action, and as agreed in the

interview, Levy, taken in light of the art available on September 24, 2003, does not teach any *in vivo* effect. In fact, no *in vivo* data was collected or discussed by Levy.

In fact, Levy conducted only *in vitro* testing of LDL samples derived from subjects adminstered β-carotene. Their results showed improved resistance of LDL to oxidation. From the *in vitro* data, Levy predicted *in vivo* patient outcomes, but never did demonstrate the validity of their prediction. However, studies disclosed subsequently clearly undermine, and teach away from, Levy's prediction.

In fact, Levy's prediction, based on their *in vitro* LDL data and other published articles, was later shown to be incorrect in predicting of *in vivo* clinical outcomes relating to vascular disorders. Subsequent to Levy and prior to the filing date of the present application, antioxidant supplementation generally, and β-carotene supplementation in particular, was shown ineffective in effecting cardiovascular outcomes. See, e.g., Yusaf, S. et al, New England J. Med. (2000), 342:154-60 (Annex C), where treatment with an anti-oxidant such as vitamin E had no effect on cardiovascular (CV) outcome; Kritharides, L., Atherosclerosis (2002) 164:211-21 (Annex D), where it is stated that supplements of vitamin E and β-carotene "cannot be recommended" for treatment or prevention of Coronary Heart

Disease; Zureik, M. et al, Arterioscler. Thromb. Vasc. Biol. (2004), 24:1485-1491 (Annex E), where supplementation with antioxidant vitamins and minerals had no beneficial effect on carotid atherosclerosis; Jialal, I, Circulation (2003), 107:926-928 (Annex F) where it is stated that the results of prospective antioxidant clinical trials were disappointing (page 926, left-hand column, 2nd paragraph) and that the "antioxidant cocktails" have no benefit in the prevention of CVD" (page 928, left-hand column, 3rd full paragraph); Clarke, R., Cardiovascular Drugs and Therapy (2002), 16:411-415 (Annex G) where β-carotene and vitamin E supplementation showed no protective effect against cardiovascular disease; and Hegele, R.A., Current Atherosclerosis Reports (2000), 2:361-362 (Annex H), which clearly shows that vitamin E supplementation has no effect on cardiovascular outcomes.

In light of the subsequent experimental data, Levy's teaching should narrowly be drawn to β-carotene supplementation resulting in improved *in vitro* resistance of LDL to oxidation. Contrary to Levy and other's prior predictions, their data could not be extended to be predictive of any effective *in vivo* treatment of vascular disorders. Levy, thus, not only does not anticipate the present claims, but in fact, Levy's predictions are countered by the subsequent art.

**2. Rejection of Claims 1-2, 8-9, and 16-17 under 35 U.S.C. §102(b)**

Claims 1-2, 8-9, and 16-17 stand rejected under 35 U.S.C. §102(b) as being anticipated by Yoko, et al. (V). This rejection is traversed as to the present claims.

As the basis for this rejection, the Office Action states:

> Yoko teaches a method for reducing triglycerides in the plasma of a subject comprising administering an effective amount of *Dunaliella* powder comprising an approximately 1:1 ratio of all-trans β-carotene and 9-cis β-carotene to patients with hyperlipidemia. Yoko teaches, "The plasma level of total cholesterol (TC), triglyceride (TG), LDL-cholesterol (LDL), lipid peroxide (LPO) and total lipid (T-Lip) significantly decreased by the administration of *Dunaliella* powder." Yoko further teaches that *Dunaliella* powder is useful material of functional healthy food not only for hyperlipidemia, but also artheriosclerosis because the level of LPO was decreased in hyperlipidemic patients. Hence, Yoko also teaches a method for treating atherosclerosis.

Applicants' present claims are directed to "a method for increasing HDL cholesterol levels in the plasma of a subject by administrating to the subject an effective amount of crude *Dunaliella* powder."

Yoko, et al. remain silent about HDL cholesterol levels. The prior reference discloses that *Dunaliella* decreases total cholesterol, triglycerides, LDL cholesterol, lipid peroxides, and total lipids, in plasma of hypercholesterolemic mice.

More importantly, Takahashi, et al., previously cited by the Examiner teaches away from the claimed invention. Takahashi

shows that administration of *Dunaliella* extract "decreases" HDL-cholesterol. The present inventors defied the teachings of the prior art and, thus, are deserving of a patent.

In view of the above, the Examiner is invited to withdraw this rejection.

**3. Rejection of Claims 1-2, 8-10, and 16-17 under 35 U.S.C. §103(a)**

Claims 1-2, 8-10, and 16-17 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Levy, et al. (U) and Levy, et al. (W), and further in view of Yoko et al. (V). This rejection is vehemently traversed.

The Office Action states, in pertinent part:

> Applicant's arguments and the declaration of Ami Ben-Amotz filed under Rule 132 have been fully considered but they are not deemed persuasive because the cited references provide the suggestions and motivation to the claimed invention.
>
> * * *
>
> [N]owhere in the references of either Yusuf or Hegele is there a disclosure or suggestion for the administration of the claim-designated composition for the treatment of any of the claim-designated disease conditions. In other words, Applicant has relied upon nonanalogous art; the prior art references are not reasonably pertinent to the particular problem with which the Applicant is concerned.

To establish a *prima facie* case, three requirements must be satisfied.

(1) The prior art must at least suggest all claim limitations. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

(2) The prior art relied on and the art at the time of the invention must contain some suggestion or incentive that would motivate an artisan to produce a modification. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

(3) The proposed modification must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).

The above rejection fails to establish a reasonable expectation of success, when viewed in light of the art as a whole at the time the application was filed.

The Levy articles, as admitted by the Examiner, hypothesize that administering a beta-carotene containing extract of *Dunaliella bardawil* to diabetic patients will effect a significant reduction in susceptibility to LDL oxidation. Levy employ as a measure of reduction in susceptibility to LDL oxidation an increased lag time and reduction in malondialdehye (MDA) and lipid peroxides (PD). See, e.g., Levy (W), abstract, where it is stated that "Atherogenesis involves oxidative

modification of LDL, which is associated with the depletion of the LDL endogenous anti-oxidants," and "Enrichment of LDL with the anti-oxidant β-carotene has the potential of reducing the susceptibility of LDL to lipid peroxidation".

In making this obviousness rejection, the Examiner then followed Declarant Ami Ben-Amotz' and colleagues' reasoning in the Levy articles. That is that anti-oxidants protect LDL against oxidation; that β-carotene contained in *Dunaliella* acts as an anti-oxidant; and that the administration of the β-carotene in *Dunaliella* would:

(1) protect LDL from oxidation, and

(2) provide a therapeutic benefit for effectively treating atherosclerosis.

See, e.g., Levy (W), pg. 13, last paragraph. While the former was demonstrated by Levy and other "early" work discussed below, the latter has been thoroughly disproven by the "later" work also discussed below.

The above rejection is based on a hypothesis that was fully discredited and disproven by the filing date of this application. That is that atherogenesis involves LDL oxidation associated with LDL anti-oxidant depletion, and that enrichment of LDL with β-carotene reduces the susceptibility of LDL to lipid peroxidation. The above hypothesis had been shown to be patently

erroneous by the intervening art as of September 24, 2003.

"Early" work in this field is exemplified by the following articles: Abbey M, Arterioscler. Thromb. (1993), 13:590-600 (Annex B); and Dr. Ben-Amotz' work, described in Levy, et al., J. Nut. Env. Med. (1995), 5:13-22 (W) and in Levy, et al., Ann. Nut. Metab. 2000, 44(2):54-60 (U). A common thread in these four articles is that they perform *in vitro* testing of LDL samples derived from patients. No *in vivo* data was collected or discussed in any of these studies. The *in vitro* data lead to a prediction of favorable *in vivo* patient outcomes. It was this prediction of *in vivo* clinical outcomes, based on *in vitro* data, that was subsequently proven incorrect.

The "later" work in the field is exemplified by the following articles: Yusaf, S. et al, New England Journal of Medicine (2000), 342:154-60 (Annex C), showing that treatment with an anti-oxidant, such as vitamin E, has no effect on cardiovascular outcomes; Kritharides, L., Atherosclerosis (2002) 164:211-21 (Annex D), which clearly states that supplements of vitamin E and β-carotene cannot be recommended for the treatment or prevention of Coronary Heart Disease; Zureik, M. et al, Arterioscler. Thromb. Vasc. Biol. (2004), 24:1485-1491 (Annex E) which observes no beneficial effects on carotid atherosclerosis of antioxidant vitamin and mineral supplementation; Jialal, I,

Circulation (2003), 107:926-928 (Annex F) finds utter disappointment in the results of prospective antioxidant clinical trials (page 926, left-hand column, 2nd paragraph, and further states that it is clear that the antioxidant cocktails have no benefit in the prevention of CVD (page 928, left-hand column, third full paragraph)); Clarke, R., Cardiovascular Drugs and Therapy (2002), 16:411-415 (Annex G) stating that multiple clinical trials failed to show protection against cardiovascular disease (3 large-scale trials of β-carotene supplementation involving 70,000 people and 5 large-scale trials of vitamin E supplementation involving 29,000 patients failed to confirm any protective effect for cardiovascular disease); and Hegele, R.A., Current Atherosclerosis Reports (2000), 2:361-362 (Annex H), showing that vitamin E supplementation had no effect on cardiovascular outcomes.

It is thus apparent that, as of the filing date of this application, it was patently clear that the Levy hypothesis was incorrect. Further, the Levy prediction of β-carotene obtained from crude Dunaliella powder being useful in the therapeutic treatment of diabetes mellitus and atherosclerosis had also been proven wrong. In view that antioxidants lack efficacy in the treatment of cardiovascular diseases, Levy's conclusions would have been disregarded by an artisan in favor of "later" *in vivo*

studies.

Thus, based on the showings that vitamin E and β-carotene supplementation has "*no* therapeutic effect" on cardiovascular disease, it would have been expected at the time this application was filed that crude *Dunaliella* powder "would not have a therapeutic effect" as a result of its anti-oxidant content (the active agent in the crude Dunaliella powder used in the invention is β-carotene) See, for example, the paragraph bridging pages 1 and 2 of this application. It was not only neither predictable nor obvious, but counter to the contemporaneous art at the time this application was filed, that crude *Dunaliella* powder would have an effect on atherosclerosis. It was surprising and unexpected, moreover, that crude *Dunaliella* powder in fact showed a therapeutic effect as presently claimed.

In summary, as of the filing date of this application (September 24, 2003), one of ordinary skill in the art would have disregarded Levy (U) and Levy (W) in view of the contemporary showings teaching away from Levy. Levy's disclosures and predictions on the efficacy of treating diabetes mellitus and atherosclerosis with crude *Dunaliella* powder were considered outdated and in error at the time this application was filed. The claimed invention is thus surprising, unexpected,

and counter to the contemporaneous wisdom in the art.

Levy, et al. (U) and Levy, et al. (W) do not teach or suggest the inventive subject matter. The Yoko et al. secondary reference does not remedy the deficiencies of Levy, et al. (U)and Levy, et al. (W).

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

**4. Rejection of Claims 1 and 3-10 under 35 U.S.C. §103(a)**

Claims 1 and 3-10 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Levy, et al. (U) in view of Beck, (A), Pan et al. (B), Heyman, et al. (D) and Smith (N). This rejection is traversed. The large number of references needed to provide a rejection speaks of the non-obviousness of the claimed invention.

The Office Action states, in pertinent part:

> The rejection stands for the reasons set forth in the previous Office action, the reasons set forth above, and for the reasons set forth below.
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> * * *
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> In this case, the primary reference of Levy (U) was relied upon for the reasons set forth in the previous Office action and for the reason set forth immediately above. ...[T]he secondary references of Beck, Pan, Heyman and Smith were relied upon because Beck taught a method for the treatment of normolipidaemic diabetes mellitus comprising orally administering an effective amount of bezafibrate; Pan

> taught a method of reducing the risk of or treating diabetes mellitus comprising administering an effective amount of an antihyperlipoproteinemic agent, e.g., fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate and clinofibrate in combination with a cholesterol lowering drug, ACE inhibitor, in Column 9, lines 32-58 and Pan taught administering gemfibrozil capsules either alone in combination with a cholesterol lowering drug, ACE inhibitor in the treatment of diabetes mellitus; Heyman taught a method of treating diabetes mellitus comprising administering an effective amount of a thiazolidinedione, e.g., troglitazone, BRL 49653, pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, and darglitazone, in combination with an RXR agonist to a subject; and, Smith taught a method of treating diabetes mellitus comprising administering rosiglitazone.
>
> * * *
>
> From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicants respectfully traverse this rejection for the reasons. Levy, et al. (U) and Levy, et al. (W) were discussed above and fail to teach the claimed method. One of ordinary skill in the art would disregard the Levy references for the stated reasons. Moreover, the Shaish Declaration (filed October 4, 2004) provides further experimental results showing that the combination of *Dunaliella* powder with a PPARγ agonist (rosiglitazone) unexpectedly improves the treatment of diabetes

when compared with either component alone. The claims are believed to be patentable over the Levy references.

The Beck, Pan, et al., Heyman, et al., and Smith secondary references were briefly described by the Examiner. Clearly, they do not remedy the deficiencies of Levy, et al. (U).

The Examiner is therefore invited to withdraw this rejection.

**5. Rejection of Claims 1 and 8-10 under 35 U.S.C. §103(a)**

Claims 1 and 8-10 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Levy, et al. (U) and Levy, et al. (W) in view of Pan, et al. (B), Craig, et al. (P) and Druzgala, et al. (E), and further in view of Yoko et al. (V). This rejection is traversed.

As the basis for this rejection, the Office Action states:

> [T]he combined teachings of Levy (U) and Levy (W) were relied upon for the reasons set forth in the previous Office and for the reasons set forth above, and with particular to the teachings of Yoko as set forth above herein. Because the combined teachings of Levy (U and W) taught the claimed method for treating diabetes mellitus and atherosclerosis for the instantly claimed ingredients, as further evidenced by the teachings of Yoko as set forth above, the secondary references of Pan, Craig and Druzgala were relied upon because Pan taught a method of reducing the risk of or treating diabetes mellitus comprising administering an effective amount of an antihyperlipoproteinemic agent, e.g., fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate and clinofibrate, either alone or in combination with a

cholesterol lowering drug, ACE inhibitor, and in Column 4, lines 27-34, Pan further taught that the ingredients of his invention prevent the onset of coronary artery disease and prevent the onset of atherosclerosis in mammalian species; Craig taught a method of treating diabetes mellitus and diabetes mellitus related disease conditions, e.g., atherosclerosis, comprising administering rosiglitazone; and, Druzgala taught methods of treating disorders, such as diabetes, atherosclerosis, hypercholesterolemia, and hyperlipidemia, comprising the administration of a therapeutically effective amount of a thiazaolidinedione, i.e., troglitazone (for example, REZULIN), pioglitazone, and rosiglitazone.

...[T]he Shaish' disclosure is not commensurate in scope to the limitations of the claimed invention as the claimed invention is directed to a method for treating diabetes mellitus comprising administering to a subject an effective amount of the claim designated ingredient in together with one or more activators of nuclear receptors vs. a method for improving treating diabetes mellitus comprising administering to a subject an effective amount of crude *Dunaliella* powder together with one or more activators of nuclear receptors.

* * *

Thus, at the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add the instantly claimed ingredients to the method for treating diabetes mellitus and atherosclerosis taught by the combined teachings of Levy (U and W) to provide the claimed method of treatments... . Thus, the claimed invention is no more than the combining of old and well-known ingredients used in well-known methods of treating the claim-designated disease conditions comprising the administration of the claim-designated ingredients.

* * *

> From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Levy, et al. (U) and Levy, et al. (W) were discussed above, as was the subsequent art. Neither reference teaches the claimed method for treating diabetes mellitus. One of ordinary skill in the art would disregard the Levy references. Moreover, the experimental results of the Shaish Declaration show that the combination of *Dunaliella* powder with a PPARγ agonist (rosiglitazone) provides an unexpected improvement in the treatment of diabetes when compared with either component alone.

In view of the above, it is beleived that the claimed method is patentable over the cited art. Neither Levy, et al. (U) nor Levy, et al. (W), alone or in combination, teach or suggest the inventive subject matter.

Pan, et al., Craig, et al., Druzgala, et al., and Yoko et al. described above by the Examiner, fail to remedy the deficiencies of Levy, et al. (U) and Levy, et al. (W).

The Examiner is invited to withdraw this rejection.

**6. Rejection of Claims 1-2, 8-10, and 16-18 under 35 U.S.C. §103(a)**

Claims 1-2, 8-10, and 16-18 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Yoko, et al. (X) in view of Levy et al. (U). This rejection is traversed.

As the basis for this rejection, the Office Action states:

> Yoko teaches the claim-designated methods except for wherein the powder is encapsulated. However, it would have been obvious to one of ordinary skill in the art to modify the method of disease treatment taught by Yoko by administering the reference powdered extract of *Dunaliella bardawil* in an encapsulated form to provide the claimed invention because at the time the invention was made it was known in the art of pharmacy that the oral administration of the claim-designated algal composition in an encapsulated form was conventional, as evidenced by the teachings of Levy set forth above. At the time the invention was made, one of ordinary skill in the would have been motivated and one would have a reasonable expectation of success to modify the method of treatment taught by Yoko by administering the reference powdered extract of *Dunaliella bardawil* in an encapsulated form to provide the claimed invention because Levy teaches that the oral administration of *Dunaliella bardawil* provides a mean of delivering the therapeutic algal composition. Thus, the claimed invention would have been merely a matter of judicial selection to one practicing the invention to pick and choose the form for the oral administration of the referenced algal compositions to effect a result variable for the treatment of the claim designated disease conditions, since at the time the invention was made Yoko teaches that the oral administration of effective amounts of a powdered extract of *Dunaliella* had therapeutic effects for the claim-designated disease condition, and given that Levy teaches that the encapsulation of a powdered extract of the claim-designated algal extract has therapeutic beneficial effects.

> According, the claimed invention was prima facie obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Yoko, et al. and Levy, et al. (U) were discussed above. Neither Yoko, et al. nor Levy et al. (U), alone or in combination, teach or suggest the claimed invention.

Thus, the Examiner is cordially invited to withdraw this rejection.

**7. Rejection of Claims 1-18 under 35 U.S.C. §103(a)**

Claims 1-18 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Yoko et al. (V) and Levy et al. (U) in view of Beck (A), Criere, et al. (O), Clark, et al. (C) and Heyman, et al. (D). This rejection is traversed.

As the basis for this rejection, the Office Action states:

> The combined teachings of Yoko and Levy teach the claimed invention except for the instantly claimed one or more activators of nuclear receptors. However, it would have been obvious to one of ordinary skill in the art to add the instantly claimed ingredients to the methods for reducing triglycerides and/or increasing HDL cholesterol levels in the plasma of subject taught by the combined teachings of Yoko and Levy to provide the claimed method of treatment... . Firstly, in Column 1, lines 11-16, Beck teaches that the administration of bezafibrate is widely used for the treatment of hyperlipidaemias (hypertriglyceride-ciaias and hypercholesterolaemias); Criere teaches a method of treating hyperlipemia, including hypercholesterolemia and hypertriglyceridemia, comprising the administration of an effective amount of fenofibrate; and Clark suggests that the

> administration of clofibrate, gemfibrozil, fenofibrate and bezafibrate reduce serum cholesterol. Secondly, Heyman teaches a method of treating hypertriglyceridemia comprising administering an effective amount of a thiazolidinedione, e.g., troglitazone, BRL 49653, pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, and darglitazone, in combination with an RXR agonist to a subject. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add the instantly claimed ingredients to the methods for reducing triglycerides and/or increasing HDL cholesterol levels in the plasma of subject taught by the combined teachings of Yoko and Levy to provide the claimed method of treatment because Criere, Beck and Clark teach that the claim-designated fibrates are effective in lowering serum cholesterol; and, in Column, 2, lines 5-11, Heyman teaches that the combination of an RXR agonist and a PPARγ agonist, i.e., a thiazolidinedione, achieves synergistic action of the RXR/PPARγ heterodimers so as to enhance adipogenic and antidiabetic effects of PPARγ. Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add any of the claimed ingredients in the making of the claimed method because it is well known that its prima facie obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art.

Yoko (V) and Levy (U) were discussed above. Neither Yoko (V) nor Levy (U), alone or in combination, teach or suggest the claimed invention.

Beck, Criere, Heyman, and Clark were also discussed above. None of these references, alone or in combination, remedies the deficiencies of Yoko (V) and Levy (U).

Accordingly, the Examiner is invited to withdraw this rejection.

**CONCLUSION**

Based upon the above remarks, the presently claimed subject matter is believed to be novel and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the rejections of claims 1-18 and allow all pending claims presented herein for reconsideration. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if she has any questions or comments.

Respectfully submitted,

**NATH & ASSOCIATES PLLC**

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